
Role of Red Complex Pathogens in The Development of Cardiovascular Diseases

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Abstract: The pathophysiology of cardiovascular disease (CVD) includes inflammation which ultimately leads to the development of atherosclerosis and thrombosis. Increasing evidence supports oral infections and in particular the common periodontal diseases, to be associated with CVD development. Periodontal infections are common worldwide and in moderate to mild form in about 35% population according to the World Health Organization. The aim of this study is to present a brief review of recent literature available on the association of red complex pathogens in development of CVD. A brief description of oral bacteria, periodontal diseases, atherosclerosis, underlying pathophysiology has been included. There is growing evidence on the association of periodontal diseases and CVD as given by epidemiological studies. The relationship between periodontal red complex pathogens and CVD deserves further research because of its consequences for public health.

Keywords: Cardiovascular diseases; red complex pathogens; atherosclerosis; periodontal diseases; gingivitis

INTRODUCTION

Cardiovascular disease (CVD) has been the leading cause of death for more than a hundred years (Leishman, Do and Ford, 2010). They have serious health implications in most countries of the world and are regarded as the most frequent systemic problem affecting the general public (Grossi *et al.*, 1995). There are many risk factors associated with CVD including tobacco use, alcohol consumption, hypertension, high cholesterol, unhealthy diets and obesity. As the number of risk factors increases, the likelihood of contracting CVD also increases. The majority of these risk factors are 'modifiable risk factors' and altering lifestyle events can drastically reduce the risk of CVD (Inaba and Amano, 2010). Cessation of smoking, carrying out regular exercises and changing to a healthy diet can significantly cut down the risk of CVD. Amongst the non-modifiable risk factors are age, gender, family history and ethnic origin (Madianos, Bobetsis and Kinane, 2002). Red complex pathogens (*Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*) are implicated in the pathogenesis of periodontal disease (Ghoury, Preiss and Sattar, 2010). In individuals with good periodontal health a very shallow space known as gingival sulcus is maintained around the circumference of the tooth surface by the gingival tissues (Chen *et al.*, 2012; Shahana and Muralidharan, 2016). In a diseased state, microorganism present in the gingival sulcus actuates the inflammatory process, which causes the deepening of the sulcus, which generally develops into periodontal pocket, follows a series of events beginning with gingivitis, apical migration of gingival attachment and loss of connective tissue and alveolar bone. It has been suggested that such inflammatory processes of periodontal tissues may directly or indirectly influence the genesis of systemic disease such as CVD (Ashwin and Muralidharan, 2015).

Several studies have developed epidemiological links between periodontal diseases and CVD, establishing association between these two different diseases (Cotti *et al.*, 2011; Pratha, Ashwatha Pratha and Geetha, 2017). Sugar in the diet is an important substrate for bacteria, viruses and fungi which can be included in the biofilm, dental plaque of oral cavity. Infectious agents include over 700 bacteria. Most common viruses are *Herpes Simplex Virus type 1* (HSV-1), *Cytomegalovirus*, *Human papillomavirus* (Marickar, Geetha and Neelakantan, 2014; Mysak *et al.*, 2014). The American Health Association (AHA) provided guidelines on the periodontal diseases as one of the less well documented or potentially modifiable risk factors with a risk estimate for those in the age group of 27-74 years (Girija *et al.*, 2019), (Thakare, Deo and Bhongade, 2010). A systematic

literature review in 2007 on association between periodontal and chronic heart disease reported in meta analysis a relative risk in prospective studies of 1.5 and odd ratio of case control studies of 2.23. Later publications summarise the more recent development as there are an increasing number of studies now being published on association between oral infection and CVD (Selvakumar and Np, 2017; Vaishali and Geetha, 2018). A joint workshop of European federation of periodontology and American academy of periodontology, on periodontitis and systemic diseases took place and concluded about 3 major issues (a) epidemiological evidence shows that periodontitis increase the risk of CVD (Carrouel *et al.*, 2016), (b) impact of periodontitis on atherosclerotic CVD is biologically plausible because circulating oral microbiota directly or indirectly induce inflammation impacting the pathogenesis of atherosclerosis, (c) interaction and biological mechanisms have been shown in animal in vitro and clinical studies which support those mechanisms in atherosclerosis. Our team has rich experience in research and we have collaborated with numerous authors over various topics in the past decade (Deogade, Gupta and Ariga, 2018; Ezhilarasan, 2018; Ezhilarasan, Sokal and Najimi, 2018; Jeevanandan and Govindaraju, 2018; J *et al.*, 2018; Menon *et al.*, 2018; Prabakar *et al.*, 2018; Rajeshkumar *et al.*, 2018, 2019; Vishnu Prasad *et al.*, 2018; Wahab *et al.*, 2018; Dua *et al.*, 2019; Duraisamy *et al.*, 2019; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Gheena and Ezhilarasan, 2019; Malli Sureshbabu *et al.*, 2019; Mehta *et al.*, 2019; Panchal, Jeevanandan and Subramanian, 2019; Rajendran *et al.*, 2019; Ramakrishnan, Dhanalakshmi and Subramanian, 2019; Sharma *et al.*, 2019; Varghese, Ramesh and Veeraiyan, 2019; Gomathi *et al.*, 2020; Samuel, Acharya and Rao, 2020)

MATERIALS AND METHOD

Study setting was made by a sampling review. Number of articles taken were 25 articles. Search engines used were 'Google scholar' and 'PUBMED'. Search terms used were related with Red Complex Pathogens' role in CVD development. There are five steps selecting an article. They were Identification of clear subjects, Identification of relevant articles, Selection, Data extraction and Charting, Analysis and Report. The articles selected based in recent similar and relevant publications. Article selection includes articles with recent advancement in associations of red complex pathogens and in developing CVD. Scoring was done for all 25 articles.

The lethal combination

Cardiovascular diseases or total cardiovascular diseases include rheumatic fever/heart diseases, hypertensive diseases, ischemic and diseases of pulmonary heart diseases and diseases of pulmonary circulation, other forms of heart diseases, cerebrovascular disease, atherosclerosis, other diseases of arteries, arterioles and capillaries, diseases of veins, lymphatics and lymph nodes not classified elsewhere as well other and unspecified disorders of circulatory system (Shahzan *et al.*, 2019), (M, Geetha and Thangavelu, 2019). When data was available, congenital cardiovascular defects were also included (AHA). Periodontal diseases include gingivitis and periodontitis. These inflammatory diseases involve the tissues surrounding and supporting teeth in mouth, which usually begins with the inflammatory process in the gums causing gingivitis and subsequently progresses to periodontitis. Periodontitis is a local inflammatory process triggered by bacterial insults which brings destruction of periodontal tissue (Kadowaki *et al.*, 1998). An interesting hypothesis suggested in some studies that oral bacteria or their metabolic products directly affect the endothelium by stimulating the formation of atherosclerotic plaques. Samples from atheromatous plaque collected from variable vascular locations contained oral bacteria or their products. The initiating factor in the CVD was the endothelial dysfunction (Priyadharsini *et al.*, 2018b), (Hujoel *et al.*, 2001). A randomised controlled trial of aggressive periodontal treatment reflected marked progress of blood flow mediated dilation pointing to an association of periodontal diseases with dysfunction of endothelial disease as a marker of early plaque formation in subjects affected by moderate to severe periodontal diseases (Wu *et al.*, 2000).

Role of red complex pathogens in CVD

Oral cavity of a newborn infant does not contain bacteria. The rapid colonization by microorganisms is a common observation during the course of development. Interestingly, by the time adulthood is reached, the oral cavity hosts more than one billion bacteria. In the form of oral biofilm the microbial flora has anatomical access to the vasculature of periodontium which contributes to extra oral spread of bacteria to sites such as the heart (Seinost *et al.*, 2005). Some studies have shown that increased antibody titres to bacteria involved in periodontitis exists in patients with CVD (Bullon *et al.*, 2011). An infection caused by *P. gingivalis* has systemic inflammation with calcification of aortic atherosclerotic plaques. It was also observed that increasing the time of exposure to pathogens stimulated the amount of calcification. Such studies highlight the presence of periodontal pathogens in CVD plaques. Although the exact underlying mechanism remains unclear (Persson and Rutger Persson, 2003; Smiline, Vijayashree and Paramasivam, 2018), a hypothesis suggests that oral bacteria contribute to endothelial dysfunction by direct invasion of endothelial vasculature. Endothelial dysfunction is associated with cell adhesion, pro inflammatory cytokines, all of which have been shown to be stimulated by *P. gingivalis*

(Linden, Herzberg and on behalf of working group 4 of the joint EFP/AAP workshop, 2013), (Buhlin *et al.*, 2002). The above mentioned studies demonstrate that periodontal microorganisms invade the endothelial vasculature. However it still remains uncertain whether they directly influence over atherosclerosis or affect already compromised endothelium.

Periodontal intervention against atherosclerotic vascular diseases

It is yet to be established whether periodontal treatment strategies alter the progression of CVD. Therapeutic strategies to combat periodontal diseases include mechanical debridement, especially of subgingival locations of the tooth and subsequent oral hygiene methods includes brushing and flossing (Kozarov, 2012; Girija, Jayaseelan and Arumugam, 2018). An investigation called the periodontitis and vascular event study (PAVE) conducted to investigate whether treatment of periodontal disease has any impact over the risk of CVD, revealed that adverse events occurred with similar incidence in community control groups and groups that received periodontal interventional treatment (Paramasivam, Vijayashree Priyadharsini and Raghunandhakumar, 2020) (Beck *et al.*, 2008). A recently published study has revealed more extensive mechanistic detail on localized oral infectious which increases systemic inflammation and oxidative stress, exacerbating CVD which contributes to future events or decreases in the threshold for CVD events (Haraszthy *et al.*, 2000).

Management of periodontal disease

Having poor oral health puts a person at risk for CVD. If gums are inflamed due to *P.gingivalis* can get into the bloodstream causing arteries to build up plaque & harden. Damaging impaction arteries & blood vessels can lead to hypertension and increase risk for strokes (Website, no date), (Reyes *et al.*, 2013). In patients with healthy gums, occurrence of gingivitis can be prevented. A daily use of antiseptic with cetylpyridinium chloride is recommended which prevents and helps in treating gingival inflammation and bleeding from gingivitis and controlling the level of periodontal red complex pathogens (Schenkein and Loos, 2013). Teaching oral hygiene (brushing technique, interproximal hygiene etc). Periodontal disease is a risk factor for the future development of CVD. By the prevention and treatment of periodontal diseases the risk of cardiovascular disease can be reduced (Meurman *et al.*, 2003). With the pursuit of understanding CVD occurrence there was now strong interest in oral infections as part of the causal pathway for CVD. There is much evidence across disciplines from basic science including Microbiology, Genetics, Pathology and other prospective studies on oral health parameters associated with incidence and mortality of CVD, through clinical trials for effect of treatment of oral infections on reducing level of CVD biomarkers in both primary and secondary prevention (Linden, Lyons and Scannapieco, 2013; Priyadharsini *et al.*, 2018a). The effect of periodontal treatment has been evaluated against known CVD biological biomarkers. Presence of a range of bacteria and viruses has been detected in CVD structures. These results indicate a scope for prevention of CVD through already well established advice for optimal oral health (Joshapura *et al.*, 2003). Our institution is passionate about high quality evidence based research and has excelled in various fields (Pc, Marimuthu and Devadoss, 2018; Ramesh *et al.*, 2018; Vijayashree Priyadharsini, Smiline Girija and Paramasivam, 2018; Ezhilarasan, Apoorva and Ashok Vardhan, 2019; Ramadurai *et al.*, 2019; Sridharan *et al.*, 2019; Vijayashree Priyadharsini, 2019; Chandrasekar *et al.*, 2020; Mathew *et al.*, 2020; R *et al.*, 2020; Samuel, 2021)

CONCLUSION

Hence, it is considered that within the limits of the review red complex pathogens influence the periodontal diseases which induce the development of CVD. Further research in this field is warranted to establish the effect of treating oral infections to prevent CVD using a randomized control study because of its consequences for public health.

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